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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/048,072	01/25/2002	Genoveffa Franchini	1662.018US1	1664

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SCHWEGMAN, LUNDBERG & WOESSNER/NIH
PO BOX 2938
MINNEAPOLIS, MN 55402-0938

EXAMINER	
PARKIN, JEFFREY S	

ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/048,072	FRANCHINI ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,9,12-17,21 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,9,12-17,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/09/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Office Action

37 C.F.R. § 1.114

A request for continued examination under 37 C.F.R. § 1.114, including the fee set forth in 37 C.F.R. § 1.17(e), was filed in this application after final rejection on 09 June, 2008. Since this application is eligible for continued examination under 37 C.F.R. § 1.114, and the fee set forth in 37 C.F.R. § 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R. § 1.114. Applicants' submission has been entered.

Status of the Claims

Claims 1-3, 9, 12-17, 21, and 22 are currently under examination.

37 C.F.R. § 1.98

The information disclosure statement filed 09 June, 2008, has been placed in the application file and the information referred to therein has been considered.

35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 9, 12-17, 21, and 22 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to

particularly point out and distinctly claim the subject matter which applicant regards as the invention. Two separate requirements are set forth under this statute: (1) the claims must set forth the subject matter that applicants regard as their invention; and (2) the claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant. The claims have been amended to simply recite "A method comprising" without providing any further details concerning the nature or purpose of the method. The method steps simply disclose a process wherein $CD8^+$ and $CD4^+$ proliferative responses are stimulated. However, the method steps fail to provide any positive correlative steps (i.e., wherein said administration results in a therapeutic anti-HIV response). Appropriate correction and clarification are required.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1-3, 9, 12-17, 21, and 22 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the

invention. The claims have been amended to simply recite a "method" that involves the administration of recombinant pox virus vectors encoding HIV-1 structural proteins (e.g., Gag, Pol, or Env) to a human patient for the purpose of inducing a $CD8^+$ and $CD4^+$ antigen-specific immune response. Additional claim stipulations require the composition to be administered to patients with viral loads <10,000 copies per ml of plasma and $CD4^+$ cell counts >500 cells/ml. The claims also encompass reductions in viral load by administering compounds that induce HIV-1-specific CTL responses.

The specification clearly states (see p. 1) that "This invention relates to an improved method of maintaining an **immunoprotective** response in persons infected with a retrovirus after highly active antiretroviral therapy (HAART)." Under the SUMMARY OF THE INVENTION the first paragraph also specifies that "The method comprises administering a nucleic-acid based vaccine, which enters the cells and intracellularly produces HIV- or HTLV-I-specific peptides for presentation on the cell's MHC class I molecules in an amount sufficient to stimulate a **protective** $CD8^+$ response." Thus, it appears the purpose of administering these compounds is to provide a therapeutic response.

As previously set forth, the legal considerations that govern enablement determinations pertaining to undue experimentation have been clearly set forth. *Enzo Biochem, Inc.*, 52 U.S.P.Q.2d 1129 (C.A.F.C. 1999). *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988). *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual

inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The disclosure fails to provide sufficient guidance pertaining to those HIV or retroviral immunogens that are capable of inducing therapeutic HIV-specific $CD8^+$ immune responses. The claims are broadly directed toward any recombinant viral vaccine encoding a peptides obtained from HIV or retroviral Gag, Pol, Env, or Nef proteins. The disclosure fails to provide sufficient guidance pertaining to the molecular determinants modulating therapeutic HIV-specific $CD8^+$ immune responses. Which HIV or retroviral proteins/polypeptides contain protective CTL epitopes? Which viral constructs are capable of expressing the immunogens of interest for a sufficient period of time to induce an HIV-specific $CD8^+$ immune response of the proper specificity, titer, and duration? The claimed invention basically requires that the skilled artisan guess as to which constructs and immunogens will provide the desired immune response.

2) The disclosure fails to provide sufficient guidance pertaining to the correlates of human protection. Currently, the correlates of human protection remain to be elucidated. To date, it is not clear what type of immune response is required to provide a therapeutic benefit. As Pantaleo and Koup (2004) note (see left

col., p. 808) "There is still no direct experimental evidence...that HIV-1-specific cellular immunity prevents disease progression." There appears to be some suggestion that both polyfunctional (IL-2 and IFN-γ) $CD4^+$ and viral-specific $CD8^+$ T-cell responses are involved. The disclosure fails to address either of these considerations. Moreover, $CD8^+$ T-cell responses by definition are not protective in nature. CTL vaccines do not prevent infection, but rather control the spread of virus. As McMichael and Hanke (2003) state (see left col., p. 876) "Whereas neutralizing antibodies can prevent infection, $CD8^+$ T-cell responses cannot. These cytotoxic T lymphocytes (CTLs) react to other cells of the body that are infected by HIV and present peptide fragments of viral proteins bound to MHC class I proteins." The authors further conclude that "A vaccine should stimulate high numbers of $CD8^+$ T memory cells, which rapidly release cytokines and chemokines on subsequent antigen contact and start killing target cells (Fig. 2). But these cells may need to be expanded to out-number the virus-infected cells and distributed to several sites around the body. Thus, full antiviral activity may take days to develop and will only control, rather than prevent, viral infection." The specification is silent concerning these issues.

3) The disclosure fails to provide sufficient guidance pertaining to the *quasispecies* nature of HIV infection that ultimately leads to viral evasion and escape. The plasticity of the HIV-1 genome and its contribution to immune escape are salient factors that have prevented the development of an effective vaccine. HIV-1 exists as a large pool of genotypically and phenotypically distinct isolates. It has been well-documented that the virus relies upon this heterogeneity to escape immune surveillance and

detection (McMichael and Hanke, 2003). For instance, the majority of the neutralizing antibody response is directed toward a molecular determinant (V3) that undergoes rapid mutation. Thus, even when a neutralizing antibody or $CD8^+$ response is generated, it rapidly becomes ineffective as other members of the *quasispecies* quickly replicate and grow out. The disclosure fails to provide any guidance concerning the identification of HIV or retroviral CTL epitopes that are resistant to viral escape.

4) The disclosure fails to provide any working embodiments. As noted *supra*, the claims encompass considerable breadth pertaining to the viral construct (i.e., source of viral expression vector, HIV/retroviral immunogens expressed). The only examples provided in the specification are purely prophetic and fail to provide any meaningful data. Some data was provided from a macaque model, however, this model is not an art-recognized model for vaccine development. Although animal models, such as the macaque system, are capable of providing important information pertaining to the understanding of pathogenesis and immunity, the results from such studies cannot be directly extrapolated to a clinical setting due to the structural differences between SIV and HIV (Haigwood, 2004). As Haigwood (2004) concludes (see abstract, p. 187) "By necessity, animal models can only be validated after successful trials in humans and the determination of correlates of protection. Because the only vaccine product tested in phase III trials in humans failed to achieve the desired protective threshold, we are as yet unable to validate any of the currently used nonhuman primate models for vaccine research." Pantaleo and Koup (2004) also concluded (see right col., p. 809) that "it is also unclear what data from which animal model of HIV-1 infection are most relevant to human infection and vaccine protection."

Additional limitations pertaining to the macaque model were reviewed by Feinberg and Moore (2002) who note (see left col., p. 207) that "because HIV-1 does not productively infect macaques, it cannot be used as a challenge virus to assess whether a given vaccine can prevent or ameliorate infection[1,2]. Hence, preclinical AIDS vaccine models rarely test the identical vaccine constructs that are planned for human use. Instead, studies in rhesus macaques explore the potential protective efficacy of vaccine concepts, not the actual vaccines being developed for human trials."

5) The state-of-the-art vis-à-vis HIV CTL vaccine development can be characterized by unpredictability (Haynes *et al.*, 1996; Burton and Moore, 1998; Moore and Burton, 1999; Desrosiers, 2004; Burton and Moore, 1998; Pantaleo and Koup, 2004; Haigwood, 2004; Altes *et al.*, 2002; McMichael and Hanke, 2003; Feinberg and Moore, 2002; Stott and Almond, 1995). To date, there is not one single effective HIV CTL vaccine on the market. Several clinical trials have been conducted but in every situation, the immunogen failed to induce a long-lasting and high-titer immune response. Common problems encountered with vaccine development include the extraordinary variability, or *quasispecies* nature of HIV, the lack of an exact animal model of HIV-induced AIDS, and the lack of understanding of the correlates of protective immunity. The disclosure fails to address these concerns. Moreover, applicants are reminded that enablement is determined as of the effective filing date of the application (28 July, 1999). *Chiron Corp.* v. *Genentech Inc.*, 363 F.3d 1247, 1254, 70 U.S.P.Q.2d 1321, 1325-26 (Fed. Cir. 2004). Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show

what was known at the time of filing. *In re Gunn*, 537 F.2d 1123, 1128, 190 U.S.P.Q. 402,405-06 (C.C.P.A. 1976); *In re Budnick*, 537 F.2d 535, 538, 190 U.S.P.Q. 422, 424 (C.C.P.A. 1976).

Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

Response to Arguments

Applicants argue that the Examiner is improperly reading limitations from the specification into the claims. The claims are simply directed toward methods of inducing HIV antigen-specific $CD8^+$ and $CD4^+$ immune responses in patients with the specified viral loads and CD4+ cell counts. Accordingly, it was argued that providing references directed toward protective or therapeutic immune responses was not appropriate. As set forth in the second paragraph of the rejection, the disclosure clearly states that the whole purpose of administering the recombinant pox virus vectors to a human subject is for the sole purpose of providing a therapeutic or protective effect. The disclosure is silent concerning the generation of any other immune responses. Therefore, the references relied upon are directly relevant because they demonstrate the difficulties associated with generating a meaningful CTL response against HIV.

It was additionally argued that the Declaration provided by Dr. Franchini and supporting references (e.g., Kimloch-de Loes *et al.*, 2005; Dorrell, 2006; Tubiana, 2005; and Jin *et al.*,

2002) demonstrate that HIV antigen-specific $CD8^+$ and $CD4^+$ immune responses can be generated. The Examiner is not questioning the scientific findings in these publications. These references reasonably suggest that the administration of recombinant pox viruses encoding HIV viral antigens can induce immune responses in test subjects. However, the crux of the rejection is whether or not these immune responses are of sufficient specificity, titer and duration to lead the skilled artisan to reasonably conclude that they would provide a therapeutic or protective immune response. Nothing in these teachings addresses these concerns. Accordingly, the rejection is properly maintained.

Correspondence

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 10:30 AM to 9:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Bruce R. Campell, Ph.D., can be reached at (571) 272-0974. Direct general status inquiries to the Technology Center 1600 receptionist at (571) 272-1600. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

Applicants are reminded that the United States Patent and Trademark Office (Office) requires most patent related correspondence to be: a) faxed to the Central FAX number (571-273-8300) (updated as of July 15, 2005), b) hand carried or delivered to the Customer Service Window (now located at the Randolph Building, 401 Dulany Street, Alexandria, VA 22314), c) mailed to the mailing address set forth in 37 C.F.R. § 1.1 (e.g., P.O. Box 1450, Alexandria, VA 22313-1450), or d) transmitted to the Office using the Office's Electronic Filing System. This notice replaces all prior Office notices specifying a specific fax number or hand carry address for certain patent related correspondence. For further information refer to the Updated Notice of Centralized Delivery and Facsimile Transmission Policy for Patent Related Correspondence,

and Exceptions Thereto, 1292 Off. Gaz. Pat. Office 186 (March 29, 2005).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,

/Jeffrey S. Parkin, Ph.D./
Primary Examiner, Art Unit 1648

06 September, 2008